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Peter [GB/GB]; The Gray Cancer Institute, P.O. Box 100,  
Mount Vernon Hospital, Northwood, Middlesex HA6 2JR  
(GB).

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(74) Agent: **SRINIVASAN, Ravi, Chandran**; J.A. Kemp &  
CO, 14 South Square, Gray's Inn, London WC1R 5JJ (GB).

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(71) Applicants (for all designated States except US): **ANGIO-  
GENE PHARMACEUTICALS LIMITED** [GB/GB];  
The Magdalen Centre, The Oxford Science Park, Oxford-  
shire OX4 4GA (GB). **GRAY LABORATORY CANCER  
RESEARCH TRUST** [GB/GB]; PO Box 100, Mount  
Vernon Hospital, Northwood, Middlesex HA6 2JR (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DAVIS, Peter,  
David** [GB/GB]; Angiogene Pharmaceuticals Limited,  
The Magdalen Centre, Oxford Science Park, Oxford-  
shire OX4 4GA (GB). **NAYLOR, Matthew, Alexander**  
[GB/GB]; The Gray Cancer Institute, PO Box 100, Mount  
Vernon Hospital, Northwood, Middlesex HA6 2JR (GB).  
**THOMSON, Peter** [GB/GB]; The Gray Cancer Insti-  
tute, PO Box 100, Mount Vernon Hospital, Northwood,  
Middlesex HA6 2JR (GB). **EVERETT, Steven, Albert**  
[GB/GB]; The Gray Cancer Institute, PO Box 100, Mount  
Vernon Hospital, Northwood, Middlesex HA6 2JR (GB).  
**STRATFORD, Michael, Richard, Lacey** [GB/GB]; The  
Gray Cancer Institute, PO Box 100, Mount Vernon Hospi-  
tal, Northwood, Middlesex HA6 2JR (GB). **WARDMAN,**

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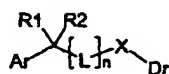
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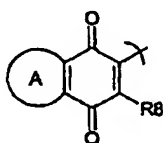
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For two-letter codes and other abbreviations, refer to the "Guid-  
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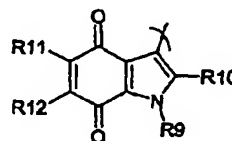
(54) Title: **BIOREDUCTIVELY-ACTIVATED PRODRUGS**



(1)



(2)



(3)

(57) Abstract: The present invention relates to a compound of formula (1), or a pharmaceutically acceptable salt thereof, wherein: Ar is a substituted aryl or heteroaryl group bearing at least one nitro or azido group or is a group of formula (2) or (3) wherein R<sub>1</sub>, and R<sub>2</sub>, which may be the same or different are independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl, COR<sub>3</sub> or, together with the intervening carbon atom, form an optionally substituted heterocycloalkyl or carbocyclic ring; L is -OC(O)- or -OP(O)(OR<sub>6</sub>)-; n is 0 or 1; X is O, S, NR<sub>7</sub> or a single covalent bond; R<sub>3</sub> is OR<sub>4</sub> or NR<sub>4</sub>R<sub>5</sub>; R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or optionally substituted alkyl or, where R<sub>4</sub> is NR<sub>4</sub>R<sub>5</sub>, R<sub>4</sub> and R<sub>5</sub> can be joined to form, together with the intervening nitrogen atom, a heterocycloalkyl ring; R<sub>8</sub> is hydrogen, alkoxy or dialkylaminoalkyl; R<sub>9</sub> is optionally substituted alkyl; R<sub>10</sub> is hydrogen, alkyl, alkoxy or dialkylaminoalkyl; R<sub>11</sub> and R<sub>12</sub> are independently hydrogen, alkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, morpholino, piperidino, piperazino or 1-aziridinyl; A is an optionally substituted aryl or heteroaryl ring; and Dr is a moiety such that DrXH represents a cytotoxic or cytostatic compound.

# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/GB2004/001330

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D333/36 C07D417/04 C07D233/54 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/06279 A (OXIGENE INC) 24 January 2002 (2002-01-24) Compound III, page 19; claim 1	1-31
X	WO 02/50007 A (CANCER RES VENTURES LTD ; HADFIELD JOHN ANTHONY (GB); HEPWORTH LUCY AN) 27 June 2002 (2002-06-27) claim 1	1-31

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Wolf, C

## INTERNATIONAL SEARCH REPORT

.....national application No.  
PCT/GB2004/001330

### Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,  
null additional fees are to be refunded.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-31 (part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-31

The claims have been searched on the basis of DrXH being combretastatin A4  
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2. claims: 1-31

The second invention is (according to preferred embodiments claimed in claim 21) the subject matter of claims 1-31 on the basis that DrXH is etoposide.  
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3. claims: 1-31

The third invention is (according to preferred embodiments claimed in claim 21) the subject matter of claims 1-31 on the basis that DrXH is cytarabine.  
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4. claims: 1-31

The fourth invention is (according to preferred embodiments claimed in claim 21) the subject matter of claims 1-31 on the basis that DrXH is 6-mercaptopurine.  
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# INTERNATIONAL SEARCH REPORT

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0206279	A	24-01-2002	AU 9621501 A WO 0206279 A1 US 2002119951 A1	30-01-2002 24-01-2002 29-08-2002
WO 0250007	A	27-06-2002	AU 1622802 A CA 2432640 A1 EP 1351912 A2 WO 0250007 A2 US 2004152629 A1	01-07-2002 27-06-2002 15-10-2003 27-06-2002 05-08-2004